

REMARKS

Claims 11-20, 22-23, 25-28, 30-32, and 44-52 are pending in the application and are presented for reconsideration. Claims 11, 15, 18, 22, 23, 27, 28, and 30-31 were amended and new claims 44-49 were added in an Amendment filed on January 16, 2003, in the parent application, but that Amendment was not entered.

New Claims

The specification provides support for new claims 44-52. Specifically, the specification recites the insertion of cPPT and CTS sequences into a previously described HIV vector in Naldini *et al.*, Science, vol. 272, pp. 263-267 (1996). See specification p. 13, lines 1-3. Naldini *et al.* describes a nucleic acid with sequences required for reverse transcription, integration, and packaging ("ψ signals", see p. 263, first column), as well as promoter sequences, such as, but not limited to, CMV, which direct the expression of a heterologous gene, by stating:

The third plasmid, the transducing vector (pHR'), contains cis-acting sequences of HIV required for *packaging*, *reverse transcription*, and *integration*, as well as unique restriction sites for the cloning of heterologous complementary DNAs (cDNAs). . . . The *Escherichia coli* β-galactosidase (β-gal) or the firefly luciferase coding sequences were inserted into pHR' downstream of the hCMV immediate early promoter to serve as reporter genes.

Naldini *et al.*, p. 263, third column (emphasis added). Furthermore, in footnote 16,

Naldini *et al.* explains:

Plasmid pHR' was constructed by cloning a fragment of the env gene encompassing the *RRE* and a splice acceptor site between the two LTRs of the HIV-1 proviral DNA. The gag gene was truncated and its reading frame blocked by a frameshift mutation.

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Id. at p. 266, FN 16 (emphasis added). Naldini et al. is incorporated by reference into the specification. Therefore, the claim elements of ψ packaging sequences, cis-acting nucleic acid sequences for reverse transcription, cis-acting nucleic acid sequences for virus integration, cPPT sequences, CTS sequences, and cis-acting RRE sequences in new claims 44-52 do not add new matter.

Applicants also note that Naldini *et al.*, as well as other references, were cited in Information Disclosure Statements previously submitted, but that they were not acknowledged by the Office. Applicants respectfully request that these references be acknowledged by initialing the Form 1449s that were submitted on January 10, 2001, and March 22, 2002.

In addition, new claim 47 does not add new matter because it was derived from original claim 13, and the terms "*Cla*I insert" and "*Eco*RI/*Bam*HI insert" were derived from the information on page 31, lines 9-11 and page 32, lines 15-18.

Finally, the term "wherein any other sequence of *pol* is absent" in new claims 50-52 does not add new matter because it is supported implicitly in the specification for several reasons. First, Figure 5A, which depicts a vector of the invention, shows that no *pol* sequences are present, nor are any *pol* sequences mention in Example 1, which describes the construction of vectors of the invention.

Second, the deposit declarations submitted with the deposit of vectors pTRIP Δ U3 CMV-GFP, pTRIP EF1 α -GFP, and pTRIP Δ U3 EF1 α -GFP, which are described in the Examples, see specification pgs. 30-31, demonstrate that these vectors are devoid of *pol* sequences. See Exhibit A.

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Third, the vector pHR' from which the vectors described in the Examples are derived, were known by those of skill in the art to be devoid of *pol* sequences. The publication Naldini *et al.*, Proc. Nat'l. Acad. Sci., vol. 93, pp. 11382-11388 (1996) (Exhibit B) explains that "[t]he *gag* gene is truncated after 350 bp and is out of frame (X), and it follows the *Rev* responsive (RRE) . . . " in the pHR' vector. See *id.* at 11383, legend to Fig. 1. This description implies that *pol* sequences are not present in the vector.

This Naldini *et al.* publication was available to those in the art because it was published in 1996, before the priority date of this application of October 12, 1999. In addition, the papers provided in Exhibits C and D demonstrate that this publication was widely known in the art. In Blomer *et al.* (Exhibit C), this Naldini *et al.* publication is cited on page 6641, col. 1, line 2. Sakoda *et al.* (Exhibit D) discusses this Naldini *et al.* publication at page 2039, col. 1, lines 10-11.

Similarly, International application WO 97/12622, Exhibit E, was available to those in the art due to its publication date of April 10, 1997, before the priority date of the instant application. This International application describes the pHR' vector as one of three vectors used to produce a recombinant retrovirus, as follows:

The invention provides a method of producing a recombinant retrovirus capable of infecting a non-dividing cell comprising transfecting a suitable host cell with the following: [1] a vector providing a nucleic acid encoding a viral *gag* and a viral *pol*; [2] a vector providing a nucleic acid encoding a viral *env*; [3] a vector providing a nucleic acid sequence encoding a packaging signal flanked by *cis*-acting nucleic acid sequences for reverse transcription and integration, and providing a cloning site for introduction of a heterologous gene, operably linked to a regulatory nucleic acid sequence, and recovering the recombinant virus.

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Id. at p. 5, paragraph 3. In this description, the pHR' vector is the third vector described. Because the first vector described contributes a *pol* gene, pHR' inherently lacks this gene.

Other publications that were available to those of art at the time of the filing of the instant application also provide information to support the lack of *pol* sequences in the vectors of the invention. Dull, *et al.*, J. Virol., vol. 72, pp. 8463-8471 (1998), Exhibit F, describes the pHR' vector as:

In either case [referring to the vector of Naldini *et al.*, Science, vol. 272, pp. 263-267 (1996), cited in the specification at pg. 13, line 1-3, for the construction of the vectors of the invention], the vector itself carried the HIV-derived *cis*-acting sequences necessary for transcription, encapsidation, reverse transcription, and integration. [citations omitted] It thus encompassed, from the 5' to 3' end, the HIV 5' LTR, the leader sequence and the 5' splice donor site, approximately 360 bp of the *gag* gene (with the *gag* reading frame closed by a synthetic stop codon), 700 bp of the *env* gene containing the RRE and a splice acceptor site, an internal promoter (typically the immediate-early enhancer/promoter of human cytomegalovirus [CMV] or that of the phosphoglycerokinase gene [PGK]), the transgene, and the HIV 3'LTR.

at 8463. From this description it is apparent that the pHR' vector lacks any *pol* sequences because none are recited in its description, while other HIV gene sequences, such as *gag* and *env*, are recited.

In addition, the deletion of *pol* gene sequences from retroviral transfer vectors is not a random feature, but a common feature of all retroviral transfer vectors needed to improve their biosafety. This feature was known by those skilled in the art at time of the filing of the application, as indicated in a later published reference. See Current Topics in Microbiology and Immunology, Exhibit G.

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Therefore, several publications available to those in the art at the time of the filing of this application describe the vector on which the claimed invention is based as lacking *pol* sequences. In summary, there is support for the claim element "wherein any other sequence of *pol* is absent" and this element does not add new matter to claims 50-52.

Claim Rejections

Claims 41 and 43 were previously rejected under 35 U.S.C. § 102(b) and 35 U.S.C. § 103 by the Office. See Office Action, Paper No. 14, pages 2-6. Applicants have cancelled claims 41-43 and respectfully request that the rejections be withdrawn.

Furthermore, claims 1 and 8-32 were rejected under 35 U.S.C. § 112, first paragraph, see Office Action, Paper No. 14, page 7, and also under 35 U.S.C. § 112, second paragraph, see Office Action, Paper No. 14, pages 8-10. The Office asserted that the reference to Figure 5A renders the claims indefinite and is not supported under the written description requirement. Applicants have cancelled claims 1, 21, and 29, which recited Figure 5A, therefore obviating the rejection. Furthermore, a description of the preparation of a nucleic acid claimed in new claims 44-46 can be found in Example 1 of the specification and in Naldini *et al.*, note 16. Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 112, first and second paragraphs, be withdrawn.

In view of the foregoing amendments and remarks, Applicants respectfully request the timely allowance of the pending claims.

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Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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